REMARKS

Applicants wish to thank Examiner Huff for taking time to conduct a telephonic interview with the undersigned representative on October 7, 2004, and are particularly thankful for her helpful suggestions regarding the amendment of claim 1.

I. Status of the Claims

Claims 1-20 were originally filed. Subsequently, claims 3-20 were canceled and new claims 21-23 were added.

Upon entry of the present amendment, claim 1 is amended to recite "being encoded by a nucleic acid capable of under stringent hybridization conditions specifically hybridizing to a polynucleotide sequence, which encodes the amino acid sequence of SEQ ID NO:2." Support for this language can be found in the specification. For instance, on page 17, lines 21-23, the specification describes that the MXR variants (in the form of nucleic acid) can hybridize with a polynucleotide sequence encoding an exemplary MXR polypeptide under stringent hybridization conditions. The term "hybridizing specifically to" is defined on page 13, lines 13-30, of the specification. The same section also provides description of the hybridization conditions. No new matter is introduced.

In addition, claim 22 is amended to ensure proper antecedent basis, and claim 23 is amended to correct a grammatical error.

II. Claim Rejections

A. 35 U.S.C. §102: Anticipation

The Examiner maintained the rejection of claims 1 and 2 under 35 U.S.C. §102(a) for alleged anticipation by the Doyle *et al.* reference and the rejection of claims 1 and 2 under 35 U.S.C. §102(e) for alleged anticipation by U.S. Patent No. 6,313,277 to Ross *et al.* Applicants respectfully traverse the rejection.

To swear behind Doyle *et al.* and Ross *et al.* (which have effective dates of Feb. 5, 1998, or later), Applicants submitted the Declaration of Drs. Michael Dean, Rando Allikmets,

Susan Bates, and Antonio Fojo under 37 C.F.R. §1.131 ("the Declaration"), which the Examiner has acknowledged shows that Applicants had possession of SEQ ID NOs:1 and 2 prior to Feb. 5, 1998 (Final Office Action of March 17, 2004, last paragraph on page 3). The Examiner asserted, however, that the Declaration has failed to swear behind the two cited references because the references disclose sequences 99.4% and 99.8% but not 100% identical to SEQ ID NO:2.

Standards Stipulated in the MPEP

Applicants do not believe that the Examiner's position is consistent with the standards set forth in the MPEP or case law, because the evidence shown in a Rule 131 declaration need not be identical to the disclosure of a cited reference. According to MPEP §715.02,

> **[A] 37 CFR 1.131 affidavit is not insufficient merely because it does not show the identical disclosure of the reference(s) or the identical subject matter involved in the activity relied upon.** If the affidavit contains facts showing a completion of the invention commensurate with the extent of the invention as claimed is shown in the reference or activity, the affidavit or declaration is sufficient, whether or not it is a showing of the identical disclosure of the reference of the identical subject matter involved in the activity.

(emphasis added)

Applicants believe that this section of the MPEP describes precisely the situation of the present case. This application relates to novel ATP-binding cassette (ABC) proteins that confer cytotoxicity resistance to cancer cells. The specification identifies, among other things, the polynucleotide sequence (SEQ ID NO:1) and the amino acid sequence (SEQ ID NO:2) of a full length ABC protein. There are various methods and techniques well known in the art of molecular and cellular biology that would allow an artisan to make variants of an exemplary ABC protein and confirm their retained functionality. The specification provides some detailed description of these methods. See, *e.g.*, description of amino acid conservative substitution is provided in the specification on page 14, line 14, to page 15, line 3; assays for mitoxantrone resistance are described on page 35, line 22, to page 37, line 2, and in Example 3 on pages 38-39. Thus, the identification of SEQ ID NOs:1 and 2 combined with the general knowledge of an

artisan is not only commensurate with but even beyond the extent of the invention as shown in the two cited references. By showing that the present inventors took possession of SEQ ID NOs:1 and 2 prior to the critical date of Feb. 5, 1998, the Declaration has in essence established the inventors' possession before that date of a genus of ABC proteins with the function of conferring mitoxantrone resistance to cancer cells, as defined by the currently pending claims.

In response to Applicants' argument, the Examiner quoted the MPEP §715.03, where it states: "[w]here generic claims have been rejected on a reference ... which discloses a species not antedated by the affidavit or declaration, the rejection will not ordinarily be withdrawn, subject to the rules set forth below, unless the applicant is able to establish that he or she was in possession of the generic invention prior to the effective date of the reference." The Examiner thus concluded that the anticipation rejection was properly sustained (the section bridging pages 5 and 6 of the Office Action mailed July 21, 2004).

Applicants do not agree with the Examiner's conclusion based on the reading of MPEP §715.02 and §715.03 in light of the particular facts of the present case. Taken together, these two sections of the MPEP clearly do not impose a strict requirement for a Rule 131 declaration to demonstrate possession of the exact same subject matter as that disclosed in a cited reference, as §715.02 states that a declaration "is not insufficient merely because it does not show the identical disclosure of the reference(s)"; rather, the requirement is a showing of "a completion of the invention commensurate with the extent of the invention as claimed" (see §715.02). To further illustrate the requirement for a Rule 131 declaration in a situation where the claim in question is a genus claim whereas the declaration and the reference concern different species, §715.03 states:

> Proof of prior completion of a species different from the species of the reference or activity will be sufficient to overcome a reference indirectly under 37 CFR §1.131 if the species shown in the reference or activity would have been obvious in view of the species shown to have been made by the applicant ... ... Alternatively, if the applicant cannot show possession of the species of the reference of activity in this manner, the applicant may be able to antedate the reference or activity indirectly by, for example, showing prior completion of one or more species which put him or her in possession of the claimed genus prior to the reference's or activity's date. **The**

> **test is whether the species completed by applicant prior to the reference date or the activity's date provided an adequate basis for inferring that the invention has generic applicability. … …**
>
> It is not necessary for the affidavit evidence to show that the applicant viewed his or her invention as encompassing more than the species actually made. **The test is whether the facts set out in the affidavit are such as would persuade one skilled in the art that the applicant possessed so much of the invention as is shown in the reference or activity. … …**

(Emphasis added)

Applicants contend that the identification of polynucleotide and amino acid sequences of an exemplary ABC protein MXR1, *i.e.*, SEQ ID NO:1 and SEQ ID NO:2, by the present inventors prior to the effective dates of the two cited references, combined with the advanced state of knowledge and available techniques in the pertinent art that would allow a skilled artisan to readily produce variant ABC proteins and verify their functionality, does provide an adequate basis for inferring the invention's general applicability. Given the general state of art and the particular fact that the species obtained by the present inventors prior to the effective dates of the two cited references, SEQ ID NO:2, has a nearly identical amino acid sequence to the species reported in the references (99.4% and 99.8% sequence identity, respectively), a person of ordinary skill in the art would be persuaded that the inventors of this application possessed a genus of ABC proteins encompassing the species shown in the two cited reference before the effective dates of the references. An inventor's declaration pursuant to 37 C.F.R. §1.132 is hereby submitted to establish this point.

Inventor's Declaration

In the concurrently submitted Rule 132 declaration, the lead inventor on this application, Dr. Michael C. Dean, attests that at the time when SEQ ID NO:1 and SEQ ID NO:2 were first obtained, the existence of naturally occurring homologues or variants of ABC proteins was known among those of skill in the art and generating man-made variants was not only contemplated but also feasible using techniques routine employed at that time (paragraph 5 of the declaration). More specifically, Dr. Dean points out that at the time when MXR1 was cloned,

artisans in the field knew of the existence of a family of human genes encoding numerous ABC proteins, which share common structural features, such as ATP-binding and transmembrane segments. In fact, the well conserved sequences within these domains had been used for cloning new ABC genes or for identifying new ABC genes from human cDNA databases. *See, e.g.*, Allikmets *et al.*, *Hum. Mol. Genet.* 1996, **5**(10):1649-1655, reference AC in the IDS submitted July 11, 2003. Thus, artisans in this field of research had already recognized that certain level of sequence variation can exist among ABC proteins without loss of function (paragraph 6 of the declaration).

Dr. Dean further states that, at the time the present inventors first cloned the coding sequence for MXR1, a variety of suitable techniques (*e.g.*, point-directed mutagenesis) had already been well established and widely in use for creating man-made variants of virtually any given protein. Functional assays were also available for verifying the biological activity of an ABC protein. The identification of the coding sequence for a new ABC protein, such as MXR1 of the present invention, combined with the known structural and functional characteristics of the ABC protein family, would therefore allow one with ordinary skill in the art to readily generate numerous variants of this protein without altering the protein's functionality (paragraph 7 of the declaration).

Dr. Dean therefore concludes that, at the time the inventors of this application first took possession of the polynucleotide sequence SEQ ID NO:1 and amino acid sequence SEQ ID NO:2, the general knowledge of the ABC gene family possessed by artisans in the field and the overall level of technical sophistication in the art of molecular biology would reasonably convince an ordinarily skilled artisan that the present inventors had in their possession a genus of ABC nucleic acids and polypeptides, which encompasses the species described by Doyle and Ross (paragraph 8 of the declaration).

Case Law

A review of the relevant case law finds further support for Applicants' position. In the case of *in re Rainer*, 156 USPQ 334 (CCPA 1968), for instance, the court considered an

appeal concerning a generic claim drawn to a process of irradiating foamed polyethylene. The PTO rejected the claim, citing a reference that disclosed irradiating polyethylene with four particular sources of free radical engendering compounds. Patent applicants Rainer *et al.* attempted to swear behind the reference by a Rule 131 declaration with evidence that they had successfully treated polyethylene prior to the effective date of the reference by using several free radical engendering catalysts that were different from those disclosed by the reference. The PTO held, and the court affirmed, that the Rule 131 declaration failed to show prior possession of the claimed broad invention, because the free radical engendering agents "vary widely in their chemical structure" and that Rainer *et al.* had not shown "generic applicability would be reasonable inference from their experiments of record." *Id*, at 337.

Another example is *in re Schaub*, 190 USPQ 324 (CCPA 1976). In this case, patent applicants Schaub *et al.* attempted to swear behind a reference that was cited by the examiner as anticipatory to a pending claim covering a genus of chemical compounds. In their Rule 131 declaration, Schaub *et al.* presented evidence that they had possession of two species prior to the effective date of the reference. The cited reference, on the other hand, disclosed a third species also belonging to the same genus of chemical compounds. The PTO deemed that the declaration was insufficient to antedate the reference and the decision was appealed to the CCPA. The court reversed the PTO's decision and reasoned that despite the different identity of the species disclosed in the reference and in the declaration, these species are adjacent homologs with minor structural differences such that one species would render another obvious. *Id*, at 326.

The present case has a fact pattern that is dissimilar to *Rainer* but more in line with *Schaub*. As already discussed above, the polypeptides disclosed in the cited references are highly similar in structure to the exemplary ABC protein the present inventors have shown to possess prior to the effective dates of the references: they share 99.4% and 99.8% sequence identity to the amino acid sequence of SEQ ID NO:2. It would be fair to say that these species are homologous to each other. Even though sequence variations in a polynucleotide or amino acid sequence are not generally considered obvious to each other, protein variants with such small changes in amino acid sequence (less than 1%) are likely to retain the same functionality,

which could be easily tested and verified according to methods known in the art well before the publication of the references. Thus, the facts set forth in the Rule 131 declaration in the present case would reasonably persuade a person of skill in the art that the inventors "possessed so much of the invention as is shown in the reference."

In summary, it is established by Dr. Dean's declaration that one of skill in the art would be reasonably persuaded that, at the time when the present inventors identified the coding sequence and amino acid sequence for MXR1, the present inventors possessed a genus of ABC proteins encompassing the species disclosed by Doyle and Ross. In accordance with the standards set forth in the MPEP and case law, Applicants submit that it has been properly established that the present inventors had in their possession a generic invention prior to the earliest effective date of the Doyle reference and the Ross patent. Therefore, the Doyle and the Ross references are not available as prior art references under 35 U.S.C. §102(a) or §102(e). Accordingly, the withdrawal of the anticipation rejections is respectfully requested.

B. 35 U.S.C. §112, First Paragraph: Written Description

The Examiner rejected claims 1, 2, and 21-23 following the amendment to claim 1 submitted by Applicants on June 2, 2004. During the telephonic interview on October 7, 2004, the Examiner indicated that the newly added language "being encoded by a nucleic acid capable of under stringent hybridization conditions specifically hybridizing to a polynucleotide sequence, the antisense sequence of the polynucleotide sequence encoding the amino acid sequence of SEQ ID NO:2," particularly the recitation of "the antisense sequence of the polynucleotide sequence encoding...," does not have support in the specification.

Upon entry of the present amendment, claim 1 recites "being encoded by a nucleic acid capable of under stringent hybridization conditions specifically hybridizing to a polynucleotide sequence, which encodes the amino acid sequence of SEQ ID NO:2," which is fully supported by the specification as pointed out in an earlier section. Applicants thus submit that the new matter rejection is overcome. Applicants again thank the Examiner for the helpful discussion and suggestions regarding this claim amendment.

C. 35 U.S.C. §112, Second Paragraph: Indefiniteness

In addition, claims 22 and 23 were also rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. The Examiner stated that these two claims appeared to be duplicates. Applicants respectfully traverse the rejection in light of the present amendment.

As amended, claim 22 recites that the polynucleotide sequence encoding SEQ ID NO:2 comprises SEQ ID NO:1, whereas claim 23 recites that the nucleic acid encoding the ATP-binding cassette protein comprises SEQ ID NO:1. The two claims are not identical in scope. The withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is hence respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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